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(54) Title: TREATMENT OF BLADDER AND GASTROINTESTINAL MASTOCYTOSIS

(57) Abstract

The present invention provides for the treatment of an individual suffering from bladder or gastrointestinal mastocytosis utilizing a serine protease inhibitor. The treatment includes the use of a corticosteroid that is administered separately or in combination. The serine proteases preferred are alpha 1–antitrypsin and secretory leucocyte protease inhibitor.

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TREATMENT OF BLADDER AND GASTROINTESTINAL MASTOCYTOSIS

Field Of The Invention

The present invention relates to the treatment of bladder and gastrointestinal mastocytosis. More specifically, there is provided the treatment of interstitial cystitis or systemic mastocytosis with serine protease inhibitors.

Background Of The Invention

Interstitial cystitis (IC) is characterized by a symptom complex which includes chronic, irritative and painful voiding symptoms that are associated with histological nonspecific chronic inflammation and cystoscopic finds of glomerulation and/or ulcers. It occurs primarily in women (10:1, female-to-male ratio), however, it has been diagnosed in children and adolescents. It is now believed that this clinical syndrome is multifactorial and involved several mechanisms. The hypothesized causes include infection, alternations in the glycosaminoglycan layer, lymphovascular obstruction, neurogenic disorders, endocrinologic disturbances, psychoneuroses, autoimmune disorders and nonspecific and nonspecific or immune-mediated inflammation. The disease is also considered by many as being related to the collagen diseases.

The presence of chronic inflammatory cells within the bladder wall of IC patients has been well recognized. Among those cells, the mast cell has been considered as potential pathogenesis of IC. Bladder mastocytosis was found in 20% to 65% of IC patients. However, the significance of bladder mastocytosis in IC has been a matter of debate, since it was also found in patients with specific

bladder diseases (transitional cell carcinoma and bladder outlet obstruction).

The gastrointestinal tract is a rich source of mast cells with an enormous surface area that permits a high degree of interaction between the mast cell and intestinal luminal contents. The active metabolic products of the mast cell influence gastrointestinal secretion, absorption, and motility through paracrine effects of local mast cell degranulation and also cause systemic effects through the release of cellular products into the blood stream. Systemic mastocytosis influences physiologic function through the systemic effects of mast cell products released from focái (e.g. bone marrow) or wide spread increases in mast cell number. Local gastrointestinal proliferation of mast cells in response to recognized (e.g., gluten in celiac sprue) or obscure stimuli can alter gastrointestinal function and induce systemic symptoms. Celiac sprue, inflammatory bowel disease, and non-ulcer dyspepsia are three examples of gastrointestinal diseases in which mast cells can be implicated in the pathophysiology of the symptoms.

Unlike the bladder, there is increased acid secretion resulting from the increase in histamine from the mast cells. In addition, there is an increase in oxygen-derived free radicals which not only cause damage to tissue but can inactivate alpha 1-antitrypsin if used in the therapy depending on the severity of the disease.

Mast cells are essential for the development of allergic hypersensibility reactions in which the mast cells activation and subsequent degranulation triggers the selection of many biologically active chemicals. Among these substances, one can include heparin, histamine, serotonin, neutral proteases (chymase, tryptase), chemotactic factors, cytokines, prostaglandins, vasoactive intestinal peptide, tumor necrosis factor, etc. These mediators might have a various role in stimulating different reactions, such as vasodilation, leukocyte infiltration (inflammation), tissue damage and nociceptive response, which are responsible for the clinical and pathological aspects in IC.

Since mast cell mediators release may be the origin of some of the symptoms and cystoscopic findings in IC, the urinary measurements of different mast cell mediators have been reported in technical journals in an attempt to identify potential diagnostic tests. Urinary excretion of histamine is not significantly increased in IC patients. However, urinary levels of methylhistamine, a major metabolite of histamine, were found to be significantly elevated in IC. Moreover, urinary measurement of tryptase, the major neutral protease (proteolytic enzyme) stored in the secretory granules of all human cells and which is the most abundantly released following activation, was greatly increased in IC patients. Thus, urinary histamine or methylhistamine and tryptase levels may be useful tools to diagnosis and to monitor the therapeutic response of any medication used in IC. Tryptase levels is the preferred method for gastrointestinal monitoring.

Alpha$_1$-antitrypsin (α_1-AT) belongs to serpin superfamily of serine protease inhibitor. It is a small glycoprotein which is mostly synthesized in the liver and has a molecular weight of 53,000 daltons. Human α_1-proteinase inhibitors are involved in the regulation of proteolysis, such as the coagulation pathway, fibrinolysis, tissue destruction by endogenous serine proteinases and inflammation.

Patent No. 5,492,889 to Lezdey et al, which is herein incorporated by reference, discloses the treatment of mast cell tumors by the administration of alpha 1-antitrypsin alone or in combination with other serine protease inhibitors.

Summary Of The Invention

The present invention provides a method of treating of mastocytosis of the bladder and gastrointestinal disease with specific reference to systemic mastocytosis.

According to one embodiment of the invention, there is provided the treatment of interstitial cystitis by the intravesical instillation of a serine protease inhibitor. More specifically, the treatment provides instilling into the bladder a composition containing an effective amount of a serine protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor (SLPI) and mixtures thereof.

Furthermore, there is provided the treatment of urinary incontinence in individuals who have interstitial cystitis or symptoms thereof.

According to another embodiment of the invention there is provided the treatment of individuals having a gastrointestinal disease associated with systemic mastocytosis by treatment with protease inhibitors which prevent the degranulation of mast cells, control the levels of tryptase and prevent or control the release of histamine. The treatment includes providing a composition in the form of an oral medication or a suppository. Preferably, a combination therapy is used to treat both the disease and the symptoms.

It is a general object of the invention to provide a composition and method for treating mastocytosis of the bladder and gastrointestinal tract.

It is a further object of the invention to provide a composition for treating individuals having the symptoms of interstitial cystitis.

It is another object of the invention to treat an incontinent individual wherein the incontinence is caused as a result of inflammation in the bladder.

It is yet another object of the invention to treat gastrointestinal problems that are related to mastocytosis.

It is still a further object to provide a method and composition for treating gastrointestinal diseases with serine protease inhibitors wherein there is hyperexcretion of histamines and basal acids.

Description Of The Preferred Embodiments

In accordance with one embodiment of the invention, there is provided a method for the treatment of individuals suffering from interstitial cystitis or symptoms thereof by the intravesical instillation of a serine protease inhibitor. The method consists of the administration an effective therapeutic amount of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte, protease inhibitor or mixtures thereof and analogs or derivatives thereof.

Accordingly, a composition containing at least about 10 mg of protease inhibitor in a suitable pharmaceutical vehicle is instilled into the bladder.

Preferably, about 20 to 40 mg of the protease inhibitor in its natural, transgenic or recombinant form is dissolved in an aqueous medium, such as a saline or buffer solution, and instilled into the bladder. A corticosteroid may be included in the treating composition. The treatment provides immediate relief of pain since the kinins and kallikreins can be controlled. The patient can be treated daily until the mast cells are reduced and under normal bodily control. In severe cases both H_1 and H_2 antagonists are required to block the effects of histamine. The composition may also include an H_1-antagonist such as hydroxyzine or doxepin or the H_1-H_2-antagonist can be administered separately.

A cocktail of protease inhibitors is particularly effective which includes alpha 1-antichymotrypsin because it can control basophil infiltration.

Serine protease inhibitors have been found to play a major role in the direct inactivation of the mediators of inflammation so that the normal healing process can be accelerated without interference from the excess of materials released at the site of inflammation. The almost immediate disappearance of pain indicates that there can be a control of the kinins as well. A cocktail of serine protease inhibitors their analogs, salts or derivatives, appears to provide the quickest healing when used in combination with a corticosteroid.

According to another embodiment of the invention, there is provided a method for treating gastrointestinal disease wherein the active metabolic products of mast cells influence gastrointestinal secretions, absorption and motility through paracrine effects of local mast cell degranulation and also cause systemic effects through the release of cellular products into the blood stream.

The method provides the oral or suppository administration of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor or mixtures thereof.

The drug can be administered in unit dosage form containing about 10 to 20 mg per day depending on the severity of the disease. The use of controlled release substances, for example, liposomes, diketopyperazine microparticles as disclosed by Patent Nos. 5,620,708 and 5,503,852 which are herein incorporated by reference, and the delivery systems of Patent No. 5,620,708 which is herein incorporated by reference.

The compositions preferably include an H_2-antagonist such as ranitidine and cimetidine and/or a corticosteroid. Since the inflammatory bowel disease can also be characterized by oxygen-derived free radicals that not only can cause discomfort but deactivate alpha 1-antitrypsin, treatment with an oxygen metabolite scavenger either separately or in combination is advantageous. The oxygen metabolite scavengers which may be used include ceruloplasmin, glutathione, glutathione peroxidase, superoxide dismutase, catalase, and the like.

The use of superoxide dismutase in the treatment of patients with ulcerative colitis and Crohn's disease supports use of its role in the invention.

It is understood that the different components used in the treatment of the diseases can be administered in a single unit dose or separately depending upon the patient and the severity of the disease. In most cases, where the patient is a child, the use of a steroid should be avoided.

Patients with sever mastocytosis may also develop significant malabsorption due to increased mast call infiltrates in the lamina propria of the small intestine and perhaps secondary to circulating inflammatory mediators. In adults 40-60 mg/d of oral steroid should accompany the treatment with the protease inhibitor.

The amount of steroid, H_1 or H_2-antagonist, and/or oxygen metabolite scavenger utilized is generally about 0.05 to 5%, preferably, about 0.5 to 2% by weight of composition in unit dosage form.

The corticosteroids which can be used in the treatment of the diseases include triamcinolone acetonide, fluroandrenolide, prednisone, beclomethasone valerate, amcinolone, dexamethasone, betamethasone valerate, halocinonide, clocortolone and hydrocortisone valerate.

The following examples further illustrate the practice of this invention, but are not intended to be limiting thereof. It will be appreciated that the selection of actual amounts of specific protease inhibitor to be administered to any individual patient will fall within the discretion of the attending physician and will be prescribed in a manner commensurate with the appropriate risk:benefit ratio for that particular patient. Appropriate dosages will depend on the patient's age, weight, sex, stage of disease and like factors uniquely within the purview of the attending physician.

Example 1

A 19 patient study of women with bladder mastocytosis was conducted for four weeks. Three of the patients were diagnosed as being urinary incontinent. The diagnosis of IC and bladder mastocytosis was considered as being mild to severe. Powdered alpha 1-antitrypsin (40 mg) was dissolved in 40 ml of saline solution. The solutions were instilled into the bladder for 20 minutes weekly for four weeks. Cystoscopy was carried out during and after filling the bladder for one minute at a pressure of 80 cm of water under spinal and general anesthesia. Bladder biopsies were carried out during cystoscopy. 24 hour collection for

measurement of creatine, methylhistamine and tryptase were taken.

The weekly studies showed a decrease of creatine, methylhistamine and tryptase. After two weeks, the incontinent patients were continent and cystoscopy showed a substantial decrease in mast cell tumor size.

Example 2

A composition for installation into bladders of patients having interstitial cystitis was prepared as follows:

Ingredients	Amount
2% saline solution	40 ml
alpha 1-antitrypsin	10 mg
triamcinolone acetonide	0.5 mg

The composition can be instilled weekly in the bladder of individuals having IC.

Optionally, an H_2-antihistamine can be included.

Example 3

The drug in liposomes that can be administered orally in order to transgress the gastric barrier and prevent disintegration in the stomach is prepared as follows.

Following the procedure of U.S. Pat. No. 4,239,754, a lipid phase made up of the three components lecithin, cholesterol and dicetyl-phosphate in a molar ratio of 7:2:1 is prepared with 2.6 g of lecithin, 4.4 g of cholesterol and 0.31 g of dicetyl-phosphate by dissolving in 50 ml of chloroform and the solution was evaporated. 0.5g of alpha 1-antitrypsin was dissolved in saline solution together with 0.1 g of superoxide dismutase and added to the phospholipids. The mixture is then subject to sonification for

10 seconds.

If desired, a corticosteroid in an amount of 0.01 g can be added to the phospholipid mixture and/or ranitidine.

The composition can be used to treat gastrointestinal disease and to treat the symptoms thereof.

What Is Claimed Is:

1. A method for treating an individual suffering from bladder or gastrointestinal mastocytosis which comprises administrating to the site of mastocytosis an effective amount of a protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor and mixtures thereof.

2. The method of claim 1 including the administration of a corticosteroid.

3. The method of claim 1 wherein the mastocytosis is intersticial cystitis and an aqueous composition is instilled into the bladder.

4. The method of claim 3 wherein said composition comprises alpha 1-antitrypsin.

5. The method of claim 1 wherein said mastocytosis is gastrointestinal.

6. The method of claim 5 including administering an H_1-antagonist, an H_2-antagonist or a mixture thereof.

7. The method of claim 5 including administering an oxygen metabolite scavenger.

8. The method of claim 7 wherein said oxygen metabolite scavenger is selected from the group consisting of superoxide dismutase, glutathione, glutathione peroxidase, ceruloplasmin and catalase.

9. The method of claim 7 including a corticosteroid.

10. The method of claim 5 wherein the protease inhibitor is administered orally in controlled release unit dosage form.

11. The composition for orally treating an individual suffering from gastrointestinal mastocytosis which comprise the combination of an effective amount of a serine protease inhibitor selected from the group consisting of alpha 1-antitrypsin, secretory leucocyte protease inhibitor and mixtures thereof, an oxygen metabolite scavenger and an H_1-antagonist.

12. The combination of claim 11 including an effective amount of a corticosteroid.

13. The composition of claim 11 in unit dosage form.

14. The composition of claim 11 including an antibasophilic amount of alpha 1-antichymotrypsin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01907

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, 38/43, 38/54, 38/55, 38/57; C07K 14/00;
US CL : 514/2; 530/350; 424/94.64, 94.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2; 530/350; 424/94.64, 94.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 97/34628 A1 (CARLSON ET AL) 25 September 1997 (25/9/97), see abstract, page 6, lines 1-5 and 34-36, page 9, lines 1-4, page 12, lines 17-18, claims.	1, 3-5 ------- 1-14
Y	US 5,492,889 A (LEZDEY ET AL) 20 February 1996 (20/02/96), see entire document.	1-14
Y	US 5,780,440 A (LEZDEY ET AL) 14 July 1998 (14/07/98), see column 2, lines 20-25.	6-8
Y	MIZON et al. Deglycosylation of α_1-proteinase inhibitor is impaired in the faeces of patients with active inflammatory bowel disease (Crohn's disease). Clinical Science. 1991, Vol. 80, pages 517-523, see entire document.	1-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHWARTZ et al. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. The New England Journal of Medicine. 25 June 1987, Vol. 316, pages 1622-1626, see entire document.	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01907

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CAPLUS, MEDLINE, CANCERLIT
search terms: gastrointestinal mastocytosis, protease inhibitor, alpha 1-antitrypsin, secratory leucocyte protease inhibitor, carticosteroid, superoxide dismutase, glutathione, catalase, inflammatory bowel disease, Crohns disease, mast cells